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To: Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Telephone 301-827-6860

Date: DECEMBER 30, 2004

Re: CITIZEN'S PETITION DOCKET NUMBER 2004P-0472

Dear FDA Officer:

The undersigned submit this addendum to citizens' petition 2004P-0472 in quadruplicate in accordance with 21 CFR 10.30 under Section 505 (j)(2)(C) of the Federal Food, Drug and Cosmetic Act, based on the authority granted by 21 CFR 314.127 (a)(8)(i) or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10 to request that the Commissioner of Food and Drugs refuse to grant final approval to ANDA 76-258 under its proposed labeling.

SPECIFIC ACTION REQUESTED:

We request that the Commissioner refuse to grant final approval to ANDA 76-258 for a generic fentanyl transdermal system under its current proposed labeling.

We, the undersigned, are submitting this addendum to our citizen's petition, Docket No. 2004P-0472, in order to clarify some of the serious misunderstandings contained in comments sent to the Commissioner of the Food and Drug Administration (FDA) by correspondents on behalf of Mylan Technologies and Noven Pharmaceuticals.

2004P-0472 SUP 1

First and foremost, as full-time practicing physicians who treat a large number of patients with severe chronic pain, there is nothing that we would like better than to be able to prescribe a safe, effective and less expensive equivalent generic form of the Duragesic transdermal fentanyl system (TFS). We both care for patients with chronic pain who are poor or who are on fixed incomes with no insurance coverage for their medications. Many of them could benefit greatly from treatment with Duragesic but they cannot use it because they cannot afford it. Even though Janssen, just like nearly all of the other pharmaceutical manufacturers, does offer a patient assistance program the income levels required to participate are set so low that many truly needy patients are excluded.

Second, contrary to some of the statements contained in the Mylan and Noven submissions, we are not employed by or affiliated in any way with Janssen Pharmaceuticals, Alza Corporation, or Johnson & Johnson. No employee or affiliate of these companies assisted, supported, or in any way encouraged us to submit our citizen's petition. To the contrary, in recent encounters Janssen executives reacted negatively to our efforts. Some even expressed anger, perhaps born of a fear that what we have done might endanger their company's marketing of its solid matrix TFS in Europe. Indeed, as noted in the Noven commentary, the citizen's petition that we submitted in October 2004, and a later one submitted in November 2004 by Alza Corporation, a Johnson & Johnson subsidiary, are ***not*** in agreement on many issues. Noven's statement depicting our efforts as collusive, based on "the congruency of these two petitions," is inaccurate and represents a gross mischaracterization of our petition.

Moreover, contrary to the Noven commentators' assertions, the timing of our submission was certainly ***not*** a part of a plot "to thwart Congress' purpose to provide less costly generic" pharmaceutical products. Rather, the timing of our petition was driven by a growing concern that, without such action, regulatory officials at FDA might not be moved to require that appropriate precautions be undertaken to insure the safety of the Mylan FTS prior to its appearance on the market. The timing of our petition was determined also by the fact that we were not able to gain access to information about the Mylan FTS until the posting of the text of the court's decision in *Alza Corporation and Janssen Pharmaceuticals v. Mylan Laboratories, Mylan Technologies and Mylan Pharmaceuticals Inc, 2004 U.S. Dist. LEXIS 4914(D Vt. March 25, 2004).*

Not having ever worked in the pharmaceutical industry, we were unaware of the secrecy surrounding the contents, sponsorship, and even the existence of ANDAs (Abbreviated New Drug Applications). For example, we learned of the existence of Noven's ANDA for a solid matrix FTS only after reading Noven's recent commentary on our petition, despite having carried out numerous searches of the FDA web site for additional correspondence and petitions regarding FTS products. We worked very hard (including nights and weekends since we're both in full-time medical practice) to prepare our petition so that the customary ninety-day period allotted for an initial response from the Commissioner would not expire before the date projected by the Office of Generic Drugs for final approval of the Mylan FTS.

We put in this time and effort to submit our petition because we have honest concerns about the heightened abuse potential of the solid-state FTS. Both of us have been strongly committed to preventing drug abuse for many years and we have acted on behalf of this commitment through our clinical, academic, and community anti-drug abuse activities. We readily admit that we are not scientists and we certainly are not lawyers. Nonetheless, we did the best we could to try to convey our sincere reservations to the Commissioner in a clear and balanced petition in which we tried to address some of the legal and scientific issues. We did this out of respect for the reviewers and for the petitioning process itself, which we feel deserves a high level of technical specificity.

We found it particularly disappointing that the Mylan and Noven commentators, having access to accomplished experts in the fields of law and science, would, instead, expend so much effort in their responses in belittling us personally, specifically by attacking our motives and personal integrity. They did so while ignoring the concerns we presented and the scientific evidence we offered to support them. Despite this, we remain open to reconsidering our views if provided with independently validated scientific evidence to back up what Mylan and Noven would have us and the FDA accept solely on face value.

Having reviewed the Mylan and Noven commentaries in detail, we continue to be concerned that the Mylan FTS may present an imminent hazard to public health and safety for reasons explained in detail in our petition. We use the term "may" because we have not had access to clinical data regarding the Mylan FTS or to any other studies that might resolve the concerns that we raised in our petition. We don't see how raising our honest concerns should earn us the accusation that we are trying to "undermine" the Hatch-Waxman amendment. While we are not experts in understanding the intricacies of the 1984 Hatch-Waxman Amendment to the Federal Food, Drug, and Cosmetic Act (FFDCA), we fully support its legislative intent to provide inexpensive generic forms of safe and effective medicines for the American public. With respect to controlled substances, however, the Hatch-Waxman Amendment did not anticipate or address the risks to public health and safety when, for example, abuse potential is influenced not by the bioequivalence of an active ingredient, but instead by the non-equivalent characteristics in the formulation and delivery of the active ingredient. This is the case of the Mylan FTS.

This issue is critical because the incidence of abuse of prescription opioid medications has been growing in the U.S. in recent years. According to studies conducted by SAMHSA (a division of the NIH), upwards of 30% of young Americans in their teens and early college years can be expected to be involved in at least one episode of non-prescribed use of a controlled medication. The abuse of prescription drugs, in general, has increased 163 percent since 1995, according to a recently released White House drug report, and is now the second leading category of drug abuse in the U.S. While the illicit consumption of ethically manufactured opioid medications dates back over 90 years, this form of drug abuse – even in the mode of "casual experimentation" -- has become far more hazardous of late because of the introduction of high-dosage opioid formulations, such as OxyContin.

We are honestly worried that the Mylan FTS will be turned into a rapid-release, high dosage opioid which will be subject to widespread abuse and diversion. Easily divertible, rapid-release formulations of any controlled drug pose significant hazards, especially for "casual abusers" such as high school and college students who may consume them in intermittent episodes before eventually maturing out of this behavior. We think that the Mylan FTS will be more of a hazard for these "casual abusers" than for "hard core" addicts. Over the course of our years as physicians, we have come to know quite a few "hard core" drug addicts. Although they are a self-destructive group, many will exhibit a surprising expertise in basic pharmacology that probably helps them to avoid some of the health hazards associated with their nonmedical use of drugs. This may explain why the incidence of abuse of certain prescription opioid formulations, such hydromorphone and meperidine tablets, which are often preferred by "hard core" addicts because of the ease with which they can be modified into injectable forms, is not reflected in databases that monitor the health-related consequence of drug abuse, such as the Drug Abuse Warning Network (DAWN). This may also explain why so many of the casualties of the OxyContin epidemic have been young people whose drug abuse might have turned out to be a transient phase, rather than a life-ending catastrophe, had they been able to survive their final unfortunate encounter with this medication.

For the reasons laid out in our petition, we are genuinely concerned that, under its current labeling, the approval of the Mylan FTS may spawn an epidemic of opioid abuse and diversion that will eclipse the recent OxyContin disaster. The crux of our petition is that, first and foremost, the safety of this new formulation must be assessed by careful clinical research conducted prior to marketing and not by a post-marketing body count of overdosed American teenagers. Secondly, the labeling of this new product should contain adequate precautions and restrictions to minimize the dangers associated with its use.

Specific response to Mylan commentaries

In his report, Dr. Govil, president of Mylan Technologies, states that our assertion that the Mylan FTS is a risk for diversion and abuse is "utterly baseless in fact." Dr. Govil states that we rely on "speculation by Mr. John Coleman, a former DEA official who has since become a member of the Janssen speakers' bureau." Mr. Coleman was an assistant administrator of the DEA. After successfully completing a 33-year career in public service, he continues to be a valued advisor to government agencies and non-governmental organizations on issues related to drug abuse. Mr. Coleman's expertise was even acknowledged by the U.S. Supreme Court, which recently accepted the filing of his *pro se* amicus curiae brief in a case involving drug abuse. According to Court officials, this was the first *pro se* amicus curiae brief accepted for filing by the Court in almost thirty years. Dr.Govil's term "speculation" mischaracterizes what is, in fact, expert opinion.

In his submission, Dr. Govil cites a meeting at DEA Headquarters on December 17, 2003, attended by experts from DEA's Drug and Chemical Evaluation Section and Mylan

officials. Dr. Govil states that he told the DEA experts attending this meeting that the Mylan FTS would be subject to less abuse than Duragesic because of the absence of a reservoir of fentanyl gel. This feature of the Mylan FTS, he stated, would prevent an abuser from being able to extract active fentanyl from the solid matrix system. Accepting that such a discussion occurred, we think that it would then be likely that the DEA officials would have raised the very logical question of what would happen if one pressed a piece of the patch against the inside of the cheek where, without a rate limiting membrane or the "baffling" effect of the stratum corneum of the skin, the solid matrix system might be expected to deliver fentanyl at a rapid rate. This certainly is true of Duragesic, which over the years has been subject to some transmucosal abuse. In any case, based on Dr. Govil's statement, we plan to request, via the Freedom of Information Act (5 USC §552, et seq.), a copy of the DEA report of this meeting and any subsequent DEA correspondence with Mylan Technologies. This should help to provide a context for Dr. Govil's statements about the DEA such as his comment that "since that meeting, DEA has never raised any concerns about the potential abuse or diversion issues arising from the Mylan FTS."

We are concerned that the impression that "DEA never raised any concerns" may be incorrectly seen as an expression of approval by the agency. It is our understanding that the DEA's role in the development of new pharmaceutical products is limited to assessing the abuse liability of FDA-approved drugs referred to the agency for scheduling under the Controlled Substances Act (CSA). Under the law, DEA has no official role in the approval process of a New Drug Application or an Abbreviated New Drug Application. The law provides exclusive authority to the FDA to approve new drugs for use in medical treatment. As part of this process, the agency's medical and scientific experts consider and weigh the risks of abuse potential, if any, in the proposed new drug. If the risks of abuse are significant or the new drug contains an ingredient that already is scheduled, the FDA will refer the new drug to the DEA for scheduling under the CSA. The referral will be accompanied by an FDA recommendation for a scheduling classification (C-II to C-V), which the DEA will generally accept without challenge. In the case of a generic form of a controlled substance, the DEA's role is perfunctory, as the generic form of a controlled substance defaults automatically to the schedule of the branded version.

Dr. Govil contends that since the FDA concluded that potential abuse issues relating to Duragesic had been successfully addressed in 1990 by minimizing the total amount of drug per dosage unit, this was equally applicable to the Mylan FTS. Is there any citable reference for this statement? How does this address our core concern that abusability will ***not*** be related solely to the presence of extractable fentanyl in the Mylan FTS but rather to the formulation of the drug in a delivery system that facilitates misuse and abuse of this product in a variety of different ways? Is Dr. Govil, in effect, advising us that FDA experts at the Office of Generic Drugs (OGD) have already made a thorough assessment of the abuse potential of the Mylan FTS and found it to be safe? If this were so, we would be happy to defer to the experts and withdraw our petition.

Dr. Govil states that our contention that placing the Mylan FTS against the inner cheek will produce a rapid release of fentanyl is false. This certainly is ***not*** the case with Duragesic. The limiting factor with Duragesic is that this route of administration is generally lethal when the gel is extracted from the patch because of the difficulty involved in partitioning the drug and measuring the dosing. Dr. Govil fails to reference clinical studies of transmucosal administration using the Mylan FTS, but instead bases his conclusion on theoretical contentions. We submit that what we have suggested is a testable question that is answerable by clinical research. It is of such importance to public health and safety as to require having the benefit of such research in the place of uninformed speculative opinion. For example, before Actiq fentanyl oralets were approved by the FDA for marketing there was legitimate widespread concern that swallowing the lozenge would either be a route of abuse or a mode of death. Instead of relying upon theoretical arguments based on what was then known about the pharmacology of fentanyl, the developers of this medication conducted a clinical experiment in which volunteer subjects swallowed fentanyl lozenges while an anesthesiologist stood by with a syringe of naloxone and a ventilator (see Streisand JB et et al *Absorption and bioavailability of oral transmucosal fentanyl citrate.* Anesthesiology 1991;75:223-9). Luckily, the researchers' underlying assumptions proved correct and the absorption of the swallowed fentanyl was not enough to cause adverse effects.

In the face of a similar threat from buccal absorption of fentanyl from the Mylan FTS, we would expect similar vigilance on the part of Mylan to confirm through clinical research what is now only a weak theoretical assumption. Even without such empirical evidence, we can make a reasonable *a priori* assumption that a motivated abuser finding the Mylan FTS unattachable to the buccal mucosa, would simply place a finger over the Mylan FTS to ensure sufficient contact between the patch and the inner lining of the cheek for the short period of time needed to achieve effect. In fact, this is precisely the way that Actiq is designed to work. The Actiq device contains fentanyl in a lozenge on a stick that delivers medication when the lozenge is rubbed across the mucosa. Contact with the mucosa is governed by the user, much in the same way an abuser might govern the buccal contact of a misused or partitioned Mylan FTS. For this reason, we have trouble understanding Dr. Govil's contention that a "moist surface" will subvert drug release from the Mylan FTS.

To be fair, Dr. Govil does cite some research on the Mylan FTS in his submission when he refers to "dissolution data." He describes an experiment in which the Mylan FTS was "placed in water at physiologic pH." According to Dr. Govil, "the Mylan FTS released *only* 15 percent of its drug in 30 minutes."(emphasis added) Assuming that the lowest dosage unit of the Mylan FTS contains a total of 2.5mg of fentanyl (which is equivalent to 2,500mcg), this means that 15 percent of 2,500 micrograms or 375mcg of fentanyl would be released from the Mylan 2.5mg FTS in a watery liquid (such as saliva) in 30 minutes. As a comparator, the lowest dose Actiq oralet releases 200mcg of fentanyl in 15 minutes. According to the Actiq package insert, 25% of the total dose (50mcg fentanyl) is rapidly absorbed from the buccal mucosa. The remaining 75% is swallowed and slowly absorbed through the gastrointestinal tract. Approximately one-third of this swallowed amount (another 50mcg) reaches the bloodstream.

We don't know about the efficiency of transmucousal transmission or gastrointestinal absorption of fentanyl released from the Mylan FTS. What we're concerned about is that nobody else might know either because no studies have been done. It is apparent that the initial amounts of fentanyl released from the Actiq oralet and the Mylan FTS placed in water are pretty close. It may be that there are characteristics of the Mylan matrix that will change the rate of transmucousal transmission. It could conceivably prove better at releasing fentanyl than Actiq. For example, we would expect that the half of the Mylan FTS surface that is expected to be exposed to view when it is worn as a skin patch (i.e. the "back" of the patch) will not release fentanyl. Because the Mylan FTS has this backing, an abuser could place the entire drug-releasing surface in contact with oral mucous membrane. In contrast, because of the way the Actiq oralet is structured with all aspects of its surface releasing drug equally (i.e. it has no "front" and "back"), most of the active surface area cannot be placed against the inner lining of the cheek at any given time.

One other issue that we should address in this context is the possibility that accelerants could easily be used to greatly increase the solubility and the rate of release of fentanyl from the matrix. We accept Dr. Govil's number of 15% total drug release into an aqueous solution in the first 30minutes of exposure. While we do not purport to be chemists, we assume that this relatively low rate of release is related to the fact that the fentanyl in the Mylan FTS is incorporated as poorly soluble fentanyl base rather than as fentanyl citrate (which is the form used in Duragesic and Actiq). While fentanyl base is poorly soluble in a watery solution, it should be much more soluble in alcohol. Having a mouthful of vodka or rum during abuse would therefore be expected to greatly accelerate release of the drug from the matrix. We would certainly be interested in hearing about the dissolution studies that were done, for example, in a glass of 151 proof rum. By adding a little lemon juice or vinegar to the rum we would expect that we could not only greatly accelerate drug release but we could also complete the conversion of base to citrate all in the mouth using edible reagents. We think that it should be fairly easy to design and carry out a study to test this hypothesis but we don't want to give the impression that we think that we are biochemists. We're just two doctors working in the heartland. If we can figure this out then we expect that others with a grounding in chemistry similar to ours – e.g. today's college freshmen – could come up with a better chemical strategy.

In 1997, as a precondition for FDA approval, the makers of Actiq were required to adopt a risk-management plan and specific labeling restrictions intended to reduce the abuse liability and marketing exposure of the oralet. Dr. Govil repeatedly says that our comparison of the Mylan FTS to the Actiq oralet is irrelevant because these two formulations of fentanyl have significant differences. One significant difference based on the information that Dr. Govil presents is that the Actiq oralet will deliver fentanyl in a watery environment for only fifteen minutes (PDR reference), while the Mylan FTS can be expected to maintain such delivery for hours. We see this as evidence of **increased** abusability that could easily lead to toxic or fatal results. Despite this, Dr. Govil somehow reaches a different conclusion when he states that, "even if the entire Mylan

FTS were placed in the mouth, the amount of fentanyl released from the system in a half hour is less than the amount delivered from Actiq."

Dr Govil goes on to state that our comparisons to Actiq are not legitimate because Actiq presents an abuse or diversion issue even "when used as designed." Our concern is that the Mylan FTS, by virtue of the fact that it is designed to contain fentanyl in a solid matrix without a rate-limiting membrane, *could* easily be converted for use just like Actiq, by patients and non-patients alike, even though such use (or misuse) is not the *intent* of the drug's manufacturers. Consider, for example, that OxyContin was not *designed* to be chewed, crushed, snorted, or injected, but it certainly has been misused and abused in all these ways, with catastrophic results for thousands of victims. Several years after OxyContin was approved, the FDA required labeling changes to reflect the heightened abuse liability of the drug when used *not* as directed. At the time, FDA officials, including Dr. Cynthia McCormick, director of the division of anesthetics, critical care and addiction drug products, said that the agency had learned a good deal from the OxyContin experience. We hope that the response to our petition will be a reflection of these lessons learned.

Dr. Govil states that our contention that the Mylan FTS can be converted into a "rapid release" system is "utterly without basis in fact." In a technical sense, he is correct. Our contention is based on what little we know about drug delivery, what little we know about the design of the Mylan FTS, and what we do know from our clinical experience as doctors (which is actually a lot). Our concerns are motivated by a good deal of practical experience with prescribing and administering powerful opioids to patients in pain, as well as caring for patients with substance abuse disorders. We know that one of medicine's cruelest ironies is that a medication that can restore one person's life may, in a different setting, ruin or even end another's. We feel strongly that a licensed drug company that markets its products to the general public has an ethical and moral obligation to ensure that its products are as safe as they can be for everybody concerned.

We hope that Dr. Govil understands that we acknowledge his expertise and intend him no disrespect. Unfortunately, we find nothing in his comments that would allay our concerns and, as a result, we must continue to request that the Commissioner deny approval of this product under its current labeling until the public can be reasonably assured that it is safe.

Response to Declaration of H. Brian Goldman, MD

Dr. Goldman is a well known and widely respected physician who practices emergency medicine in Canada where he previously also had a practice specializing in the management of chronic pain. In his declaration, he cites medical literature that indicates that the "desirability" (i.e., abuse potential) of an opioid drug is related to the ability of the formulation to rapidly increase levels of the drug in the brain. He accurately describes

how an opioid formulation that is designed to slowly release medication can be abused if it can be converted to a "quick release" form. He opines that the concerns that we detail in our citizen's petition, however, are baseless because the Mylan FTS cannot be converted into a "rapid release" form by applying the product, for example, to the inside of the cheek or to the surface of some other mucous membrane. The only evidence he cites for this is the information contained in the declaration of fellow Mylan consultant, Dr. Gordon Flynn.

To support his contention that the solid state FTS will not have an increased abuse potential, Dr. Goldman refers to "the experience" of the solid state "Durogesic SMAT," a product currently marketed by Janssen in Germany. This reference to the German experience of low abuse of the solid matrix FTS is not accompanied by a literature citation so it is difficult to evaluate. We certainly do not know the incidence of abuse of the solid matrix FTS in Germany. We also don't know whether the incidence of abuse of such a product in a foreign country can be used to predict its potential for abuse in the U.S.

Lastly, implying that the approval of a drug in Germany ensures its safety and obviates the need for a thorough consideration by our own FDA seems fraught with irony. It brings to mind our own usual simplistic response to complaints about the strict regulation of drugs and pharmaceutical marketing in this country, which is: "count the fingers on your kid and if they add up to ten, then thank God and the FDA." This is an obvious reference to past action by the FDA that involved refusal to approve thalidomide, a drug that was widely marketed and touted as safe in Germany for the treatment of anxiety in pregnant women. Tragically, it was soon found to cause severe birth defects in their babies. Of note, thalidomide is currently available in the U.S. and we have even prescribed it on rare occasion. Thalidomide can be prescribed safely today, not because of any change in the formulation of the product, but because of modifications in its labeling. If anything, the example of the thalidomide experience should encourage all parties in this matter, including Mylan, to provide as much information as possible about product safety in order to prevent avoidable tragedies to people using the Mylan FTS.

Response to Declaration of Gordon Flynn, PhD

Though we are not personally familiar with his work, Dr. Flynn is obviously a very distinguished physical chemist and pharmacologist with extensive experience in transdermal drug delivery systems. His initial declarations lay out his impressive credentials. Dr. Flynn provides descriptive information about the Mylan FTS. In his remaining declarations, he begins to specifically address some of the issues brought up in our petition. Unfortunately, after a careful review of Dr. Flynn's report, we were unable to find any data or other information that might relieve us of our primary concern that the Mylan patch or any part thereof can, and will, be abused by being placed in the mouth and held against a mucous membrane.

In declarations numbered 9 through 13, Dr. Flynn describes some of the structural features of the Mylan FTS. He confirms that the Mylan FTS was demonstrated to be

bioequivalent to Duragesic, when used as directed, and that it was initially granted final approval by the FDA's Office of Generic Drugs on November 21, 2003. As mentioned in our citizen's petition, final approval later was rescinded based on a court decision regarding the Duragesic patent in mid-2004. The current approval status of the Mylan FTS is "tentative." Dr Flynn also confirms that the Mylan FTS system contains the same total amount of fentanyl as the dose-equivalent Duragesic transdermal system. For example, the 25mcg/h dosage units of Mylan FTS and Duragesic each contain a dose load of 2.5mg of fentanyl (which, as we previously noted, equals 2,500mcg).

Declarations numbered 14 and onward begin to address some of the concerns expressed in our citizen's petition. In Declaration 14, Dr. Flynn states that our concern that the Mylan FTS can be abused as we describe in our petition belies a basic misunderstanding of the Mylan FTS and of fentanyl transdermal delivery systems, in general. In his next declaration he asserts that the Mylan FTS system remains a slow-release drug delivery system, even if cut into pieces and placed in the mouth. Dr. Flynn cites no data or technical scientific evidence to support this statement. He goes on to state that the delivery rate of the Mylan FTS is proportional to the surface area of the matrix. While we may assume this to be true (as it is with Duragesic), it fails to address our concern that delivery of the fentanyl to the bloodstream will be more rapid when the patch is applied to a mucous membrane than when applied appropriately to intact skin. In the case of the latter application, the absorption rate of the fentanyl is mediated by the stratum corneum before it reaches the capillary bed. We recognize that Dr. Flynn is not a clinician, but we must assume, nonetheless, that he is aware that capillaries and blood vessels are much closer to the surface in mucous membranes than they are in intact skin (which, incidentally, is why mucous membranes appear red). For this reason, the well-known pharmacokinetics of transdermal fentanyl application might not be a valid predictor of the rate of fentanyl absorption via the buccal mucosa.

In addition, Dr. Flynn declares that in order to deliver fentanyl efficiently through a membrane (whether a mucosal membrane or the skin), a matrix system needs to be in intimate contact with the membrane. We have no disagreement with that statement. But, then Dr. Flynn concludes by stating that the Mylan FTS "cannot do so," (*sic*) because it contains a hydrophobic adhesive that prevents it from binding to moist oral tissue. We do not know if this is the case because we have not seen any data about binding a Mylan FTS patch to a mucous membrane, such as found on the inside of the cheek, nose or even the rectum. What we do know is that in our citizen's petition we do not contend that adhesion to the mucous membrane is a prerequisite to transmucosal drug delivery.

For example, Actiq, which, like the Mylan FTS, is also a solid matrix system, rapidly delivers fentanyl efficiently without containing any adhesive or requiring any bonding with the mucosa. The patient needs only to press the device against the inside of the lining of the cheek in order to maintain contact between the solid surface of the Actiq and the mucous membrane. This is precisely what we stated in our petition would be the case if someone were to misuse or abuse the Mylan FTS by placing it in the mouth. As clinicians who have cared for many chronic pain patients with substance abuse problems, we are reasonably certain that transmucosal abusers of the Mylan FTS will not limit their

abuse to the membrane on the inside of the mouth but over time will be inserting the fentanyl matrix in their noses or rectums where, incidentally, the physical structure of the organs can ensure close physical contact between the surface of the device and the mucous membrane without the need for chemical adhesion or externally applied pressure.

In declaration number 20, Dr. Flynn begins to describe a clinical experiment with the Mylan FTS....almost. He describes his single-trial, undocumented attempt to stick a "placebo" version of the Mylan FTS patch to the inside of his own cheek -- "to no avail." We do not doubt the accuracy of Dr. Flynn's report but it raises a few questions, nonetheless, in terms of what he was attempting to demonstrate. Did he try manually to press the Mylan FTS against the inside of his cheek to see if he could maintain physical contact? Why did he choose to use a non-pharmaceutical variation of the Mylan FTS, rather than the real thing, if he was sure that it would not deliver fentanyl? Isn't this tantamount to drawing conclusions about the action of a drug from an experiment involving only the placebo?

The only conclusion one might reasonably draw from this solitary experiment is that, in the case presented, the hydrophobic adhesive of the Mylan FTS demonstrator patch did not adhere to Dr. Flynn's moist mucosa. Frankly, this has no relevance whatsoever to the absorbability of fentanyl from a Mylan FTS placed and held against the buccal mucosa.

Indeed, there are published reports that confirm that a fentanyl transdermal system can rapidly transmit fentanyl into the bloodstream when placed and held against the inside of the cheek despite its having a non-hydrophilic adhesive. These published reports are referenced in our petition (e.g., Liappis IA et al. *Oral transmucosal abuse of transdermal fentanyl.* Journal of Psychopharmacology 2004; 18:277-280), and involve the Duragesic FTS patch, not the Mylan FTS.

In declaration number 24, Dr. Flynn asserts (again, without data) that "Mylan's patch would not release fentanyl rapidly in the watery environment of the mouth," because "when placed in water at physiologic pHs, the Mylan fentanyl transdermal system released *only* 15 percent of its drug over a half an hour."(emphasis added) As demonstrated earlier in this letter, for the *smallest* dosage unit of Mylan FTS this calculates to 750mcg/hour. This constitutes a rapid release rate and supports the contentions in our petition. The information about the lipophilicity of fentanyl base, likewise, raises concern that the drug will be absorbed quickly when the matrix is pressed directly against the lipophilic cell membranes that comprise the uppermost layer of a mucous membrane.

Dr. Flynn's declarations concerning Actiq (#26 through #28) do not allay our concerns about the dangers of the Mylan FTS and do not invalidate our comparison of these two solid-matrix systems. Dr. Flynn points out that many of the components of Actiq are water soluble, but anyone familiar with this device or its label knows that only the surface that is physically applied to the mucous membrane will deliver active drug and that the amount of drug solubilized into saliva is more slowly absorbed from the GI tract or

rendered inactive by hepatic and intestinal first-pass elimination. The labeling for Actiq specifically addresses this important issue in the product's package insert:

> "Normally, approximately 25% of the total dose of *Actiq* is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of *Actiq* is divided equally between rapid transmucosal and slower GI absorption". (Ref: Actiq PI, Cephalon 2004; available at: http://www.actiq.com/pdf/Package%20Insert.pdf)

If we accept the above data as reasonably accurate for estimating the buccal absorption of fentanyl from a misused Mylan FTS, and if we accept Dr. Flynn's statement in declaration #24, that, "When placed in water at physiologic pHs, the Mylan fentanyl transdermal system released only 15 percent of its drug over a half hour," then we must conclude that even the smallest dosage unit of the Mylan FTS, containing a dose load of 2.5mg of fentanyl, will deliver a larger amount of drug over a similar period of time than the smallest dosage unit of Actiq (25% of Actiq 200mcg = 50mcg in 15 minutes; 15% of Mylan 2.5mg FTS = 375mcg in 30 minutes or 188mcg in 15 minutes). According to these calculations, the Mylan 2.5mg FTS, if placed in the mouth and held against the buccal mucosa, is theoretically capable of delivering upwards of 300 percent more fentanyl than the smallest dosage strength of Actiq, over a comparable time. Perhaps even more alarming is that, while the Actiq is designed to dissolve completely in 15 minutes, the buccal absorption of fentanyl from a misused Mylan FTS could continue for hours, easily reaching toxic or fatal levels.

Finally, we must respectfully state that the implications inherent in Dr. Flynn's final assertion (#29) are flat-out wrong. While we are not employees of Janssen, we are aware that several years ago the company informed several pain-management physicians that it was preparing to develop and test a solid-monolith fentanyl transdermal delivery system for marketing in the U.S. We also know that company executives were taken aback when confronted with strongly expressed concerns about abuse raised by knowledgeable consultants and forensic chemists. This was followed by a decision to abort the effort to introduce the solid-state FTS formulation to the U.S. market. The fact that a foreign division of Janssen is presently marketing a solid-matrix FTS outside the U.S. has no bearing on this matter and proves absolutely nothing. It is our understanding that the foreign divisions of Janssen are managed independently of the U.S. division.

From the limited amount of information that we have, the Janssen solid state FTS that is marketed in Europe is structurally similar to - and, therefore, theoretically as hazardous as - the Mylan FTS proposed for marketing here in the U.S. We do agree with Dr. Flynn that the different marketing decisions by the U.S. and European divisions present an inconsistency that we are in no position to explain. However do we not need to reconcile this apparent inconsistency in order to justify the concerns expressed in our citizen's petition. We are gratified that officials of the U.S. division of Janssen were attentive and

responsive to concerns about safety and did not hesitate to make the correct decision when confronted with evidence not unlike what appears today in our citizen's petition regarding the Mylan FTS. We also know that if Janssen was to change course and seek approval to market its solid matrix FTS in the U.S. with the same labeling as Duragesic, we would be petitioning the Commissioner to deny its approval, too.

Noven Petition

We would next like to address the petition submitted by Dr. Abrao, Mr. Mantelle, and Dr. Dugue on behalf of Noven Pharmaceuticals. While the title of their correspondence refers to our petition ("Re: Docket No. 2004P-0472....), they address both our petition *and* a separate and unrelated petition filed by Alza Corporation (Docket No. 2004P-0506). We had no part in the preparation or submission of the Alza petition. We have read the Alza petition since it was filed and posted and we disagree with several of its contentions. For example, requesting that the Mylan FTS be denied an "A-B" rating without denying its approval as a generic equivalent of Duragesic is, in our opinion, inherently contradictory. Moreover, as we certified in our citizen's petition, we prepared and submitted our petition without any input, support, or coordination with anyone employed by, or connected with Janssen, Alza, or Johnson & Johnson. We decided to write the petition about the Mylan FTS in the late summer of 2004. As previously stated, one reason for the timing is that we realized, perhaps at the last moment, that if we did not raise an objection to the approval and labeling of this potentially hazardous product, the FDA was unlikely to do so on its own.

We worked diligently to write a complete, balanced and cogent citizen's petition to express our concerns to the FDA. Despite the fact that it was difficult for us to take time away from our practices to prepare the petition, we made an effort to get it finished and submitted more than ninety days before the projected approval date of the Mylan FTS. We did this so we could reasonably expect the Commissioner's preliminary response (which according to the FDA's website, is rendered usually within 90 days of the receipt of a citizen's petition) before the decision to grant final approval is made in January 2005. The submission of the Alza petition a month later came as a complete, and somewhat unwelcomed, surprise to us.

The initial declarations contained in the Noven petition implying that we coordinated our actions with Alza in order to reap financial gain are patently false and personally insulting. Our petition truly is a "citizen's petition" because it was filed by two citizens motivated only by a concern for their patients' safety. We would welcome any scientific or medical data from Noven Pharmaceuticals, or anyone else, that might prove us wrong in our assertions.

In the following paragraphs we would like to respond to Noven's specific objections to our petition (which Noven refers to as the "instant Petition"). Because we have no involvement with the Alza petition, we will not address the parts of the Noven response that solely address issues cited in Alza's petition. The Noven respondents point out that the Alza petition, if accepted, "severely undercuts the instant Petition." We agree with

this and contend that this statement supports our assertion that there was no coordination or collaboration among the petitioners.

We must respectfully disagree with the Noven respondents' contention that the FDA has no legal authority to deny the ANDA in question. Our petition contains ample legal citations that provide authority for the Commissioner to refuse approval despite the demonstration of bioequivalence if the product is considered unsafe (see 21 CFR section 314.27 (8)(ii) (A)). The regulation simply says "unsafe" and does not specify that this is restricted to mean "unsafe to the patient for whom the drug is prescribed and who is using it as directed" as the Noven respondents contend. Abuse or misuse of FDA-approved drugs, whether by patients or non-patients, and whether used as directed or otherwise, is a matter of safety as defined by the FFDCA and numerous FDA rulings.

While the concept of "safety," as applied to an FDA-approved drug, sometimes is narrowly defined to mean "safe when used as directed," we would argue that a more expansive view of safety is appropriate in the case of controlled substances. By virtue of their being scheduled and controlled, the government recognizes that there is a potential for these drugs to be consumed by people for whom they have not been prescribed and for whom, therefore, they may pose a specific type of safety risk. By giving the FDA exclusive authority to decide which drugs are to be scheduled and which drugs are exempt from scheduling by the DEA, the Congress fully intended that abuse potential, the very basis for scheduling, be considered by the FDA during the evaluation of every NDA and ANDA. To re-frame this in a more "operational" context, if the Noven respondents had a chance to express an opinion on the final approval of OxyContin, knowing fully that the drug eventually would be blamed for numerous deaths, would they have said that the drug was safe for marketing under its original labeling and without a risk-minimization plan? Perhaps the silver lining in OxyContin's dark cloud is the fact that, as the OxyContin abuse epidemic began to spread throughout the nation, the court system moved to protect the public faster and more assuredly than the regulatory agencies. No longer does FDA approval of an NDA or ANDA protect a drug maker from product liability claims or damage claims arising from the deaths and injuries attributed, among other things, to abuse.

The Noven response repeats the contentions expressed in the Mylan commentary that our concerns about the increased abuse potential will not "withstand scientific scrutiny." With the understanding that we are not privy to information contained in ANDAs or in pre-marketing clinical trials, we ask again, where's the science? Where are the data? Nearly all of our concerns are clinically testable in healthy volunteer human subjects (e.g., see Streisand JB et al. *Absorption and bioavailability of oral transmucosal fentanyl citrate.* Anesthesiology 1991;75:223-9.). Even if there should be some reluctance to furnish us with scientific evidence, it would seem only reasonable that such evidence be furnished to the FDA Commissioner so that an informed decision can be made in the public interest. While the absence of evidence is not, by itself, evidence of absence, it surely raises the prospect that there are no scientific explanations that Mylan or Noven can offer to support going forward with final approval of the Mylan FTS under its current labeling.

In their submission, the Noven petitioners contend that the FDA cannot require a risk management plan as a condition for approval of the generic Mylan FTS. We respectfully disagree. We do assume, based on the FDA's initial approval, that the Mylan FTS has been shown to be safe and bioequivalent to Duragesic when used as directed by the appropriately selected patients. Our contention, which we believe is reasonable and we know to be clinically testable, is that in the hands of a drug abuser, the Mylan FTS will be found to be more "bioequivalent" to Actiq, than to Duragesic, if it is marketed with its present labeling.

Contrary to the assertion of the Noven respondents, there is precedence for requiring, as a condition for approval of its ANDA, a risk management plan for a generic version of a branded drug. One such precedent involves the recent approval of generic versions of controlled-release oxycodone. According to an article published March 23, 2004, by the Associated Press, titled, "FDA OKs generic versions of OxyContin," as part of the FDA's approval, it was reported that, "manufacturers Teva Pharmaceuticals and Endo Pharmaceuticals may sell generic versions of extended-release oxycodone *as long as* they include abuse warnings and other steps designed to minimize illegal use that are similar to the risk management program run by OxyContin maker Purdue Pharma."(emphasis added). An article on March 24, 2004 reported that Congressman Harold Rogers of Kentucky praised "the FDA's requirement that generic makers take risk-management efforts." In an article in "Drug Topics," dated August 8, 2004, Dr. Robert J. Meyer, who oversees the FDA's division of anesthetic, critical care and addiction drugs at the Center for Drug Evaluation and Research, "announced that Endo's and Teva's [risk management] plans must be consistent with one used by Purdue." We believe that the precedent established by the FDA's requirement for the generic form of controlled-release oxycodone to have a mandatory risk minimization plan moots any claim to the contrary made by Noven with respect to the Mylan FTS.

Much of the Noven response is similar to the Mylan response and many of Noven's objections (e.g. lack of adherence of the patch to mucous membranes, etc.) have already been addressed in this document and need not be restated. The Noven respondents appear to think that we contend that cutting their matrix FTS will affect the speed of drug delivery. We do not contend this. We think it will allow each dosage unit to be partitioned into multiple non-lethal doses that will be commercially and non-commercially distributed and repeatedly abused. By comparison, we are aware that fentanyl gel extracted from the Duragesic patch can be absorbed through the mucosa inside the cheek. A major problem for abusers who attempt this is that they have no way to partition the gel into non-lethal doses. As a result, most attempts at transmucosal abuse of the fentanyl-containing gel in Duragesic have resulted in catastrophic medical consequences, including overdose and death. This, in turn, has greatly limited the number of people willing to risk abusing this formulation of the drug.

One of Noven's pivotal, if unsupported, conclusions is that, "on the science and on the law, the Petition is simply wrong and must be denied." To the latter contention about the law, we respond that we have carefully laid out our legal arguments with appropriate

citations and we will leave it to the FDA general counsel to judge whether we are wrong in citing the clear-language text of the relevant statutes. To Noven's contention about our science being "wrong," we again ask, where are the data to support an opposing view? Why are these manufacturers so reluctant to perform some basic scientific studies that would establish whether their product is safe?

We appreciate the description of the matrix device provided by the Noven respondents and we have no reason to doubt that their matrix product is safe and effective when used as directed if the product has indeed passed the FDA-mandated suitability testing. However, we find no reassurance in Noven's statement that the "solid state matrix transdermal fentanyl system satisfies the *statutory* requirement for safety." (emphasis added). We are legitimately concerned, as we repeatedly stated in our citizen's petition, that any fentanyl product similar in design to the Noven matrix's "drug containing adhesive layer" will be capable of rapidly delivering high levels of fentanyl to the bloodstream, if misused or abused, especially if applied directly to a mucous membrane. Nowhere in the Noven statement do the respondents dispute this.

What the Noven commentators vigorously do dispute, instead, is our contention that they have a legal and ethical obligation to insure that they are producing a safe pharmaceutical product. We admire the obvious hard work and thoughtfulness that the Noven writers put into the exposition of this part of their commentary on our petition. We have read it carefully and learned a lot, but we continue, respectfully, to disagree with them. We believe that the FDA's first concern must always be for the safety and general welfare of the American people who consume and depend upon the products that they approve. If this turns out not to be the case, we are aware that many states, including one of our home states, Tennessee, have already enacted legislation to prohibit the marketing of FDA-approved pharmaceutical products that are deemed hazardous to residents and citizens of the state. An example of this was Tennessee's early prohibition of the prescribing of "Phen-fen," despite its ill-fated approval by the FDA.

Unfortunately, the Noven commentary mischaracterizes many aspects of our petition. One sterling example is Noven's citation of the "DEA's experience with Duragesic abusers' practice of freezing the [Duragesic] patch, cutting it into pieces and placing it under the tongue or in the cheek cavity for drug absorption through the oral mucosa." Noven characterizes this as "unimpeachable information," while we contend, based on the chemistry of the gel in the Duragesic formulation (which has a freezing point of approximately –50C), that this is, indeed, rather unlikely. We have been in contact with several former and active agents of DEA at meetings and while teaching at the DEA Training Academy in Quantico, Virginia, and have taken the opportunity to ask them if they had ever encountered this route of abuse. We haven't met a single agent who has, even though this mythical story is carried on a DEA website article about fentanyl. If Noven is so certain that this is an important route of abuse that it considers this "unimpeachable," why won't the Noven commentators reference their source? Also, if this is true, then why isn't the matrix FTS abusable in the same manner?

The Noven commentary concludes that "in sum there is no evidence to support the Petitioner's spurious contention that fentanyl transdermal products using a solid state matrix delivery system are subject to some heightened risk of abuse or diversion." In a sense we agree – there *is* no scientific evidence because the studies to produce such evidence have not been done. We do, however, object to the characterization of our petition as "spurious." Our petition was carefully thought out and prepared and appropriately referenced with numerous validated scientific and legal sources. We didn't spend our evenings and weekends researching and writing our petition for fun or for money. Unlike our interlocutors from Mylan and Noven, we derive no financial benefit from having worked on this petition. We submitted our petition because, as practicing physicians, parents of teenagers, and concerned citizens, we are alarmed that the introduction of a solid state FTS product may set off an epidemic of drug abuse that could eclipse that of OxyContin. As delineated in our curricula vitae, both of us have been very active for many years in voluntary community efforts to prevent or curb drug abuse. Our petition is an extension of these efforts. If the Noven respondents feel that it is in their interest to publicly and personally belittle us for these efforts, so be it. It certainly won't the first time for either of us but it surely does appear to undermine the credibility and integrity of what otherwise have been two fine pharmaceutical companies providing useful products for our patients.

Despite our obvious differences, we invite our Mylan and Noven colleagues to re-read our petition, this time with an open mind, and to consider our concerns, just as we have considered theirs. We believe that our concerns are serious enough to deserve a hearing and are prepared to request one if our petition is denied by the FDA Commissioner. The decision to issue final approval for the Mylan FTS, as labeled, should not be made on the basis of personal innuendo, insult, or mischaracterizations of motives and intentions, but on the basis of good science and professional candor and, above all, concern for the health and well-being of our fellow citizens.

This petition was prepared in its entirety by Drs. Brookoff and Voth without any outside assistance or support or the offer thereof. They take full responsibility for its contents. No employees or agents of any of the involved pharmaceutical manufacturers or government agencies were consulted or even informed as to the preparation of this petition.

ENVIRONMENTAL IMPACT

Not applicable

CERTIFICATION

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition addendum includes all information and views on which the addendum relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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